

NIH Comments on
FDA Draft Guidance for Industry:
Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers
Enrolled in Preventive Vaccine Clinical Trials (April 2005)
Docket No. 2005D-0155
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Introduction

FDA's April 2005 draft guidance *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* is intended to provide sponsors of vaccine trials with toxicity grading scale tables as a guideline for selecting the criteria to assess the severity of clinical and laboratory abnormalities in healthy adult and adolescent volunteers enrolled in clinical trials of preventive vaccines. The guidance provides tables for four categories of clinical abnormalities (local reaction to injectable product; vital signs; systemic (general); and systemic illness) and three categories of laboratory abnormalities (serum; hematology; and urine). Each category of abnormality includes one to 21 parameters displayed along one axis and four grading scales (mild, moderate, severe, and potentially life threatening) displayed on the other axis with recommended values defined for each parameter and grade. The guidance is intended to assist in the monitoring, assessing and reporting of adverse events, not to take the place of regulatory requirements related to adverse events. FDA believes that uniform criteria for categorizing toxicities can help define a study's stopping rules and improve comparisons of safety data among groups within the same study and also between different studies.

While we agree that a standardized approach to categorizing toxicities can assist in the monitoring, assessing and reporting of adverse events and improve comparisons of safety data among groups within the same study and also between different studies, NIH has a number of concerns about the draft guidance. First, the impetus for developing this toxicity scale is not made clear. Although we clearly agree that trial sponsors and investigators need to be cognizant of risks to healthy volunteers, the draft guidance does not describe a rationale and justification for a separate toxicity scale that is specific for healthy volunteers in vaccine trials, as opposed to other approaches for managing risks. Second, the scope of the guidance and whether and when it might be applicable to other kinds of trials with healthy subjects is also unclear. Third, the guidance does not take account of the broader scientific and public health issues associated with narrowing the range of participants on the basis of normal baseline values described in the toxicity scale. Nor does it give sufficient consideration to the question of how "healthy volunteer" is defined and whether the entire range of typical clinical and laboratory values that exist in the population should be included. For example, healthy individuals can have minor laboratory abnormalities that are clinically insignificant. If the baseline values elaborated in this scale become the basis for determining inclusion/exclusion criteria, many individuals with minor health conditions or clinically insignificant laboratory values may not be eligible for vaccine trials. The selection of study populations and setting of inclusion/exclusion criteria have significant implications for external validity and generalizability of study findings as well as

being relevant to safety concerns of participants during a trial. Vaccine research often addresses critical public health needs; because of the urgency of developing adequate prevention methods for at-risk populations, clinical trial guidelines should be constructed with a careful balance of caution and flexibility.

For these and other reasons discussed below, we recommend that, before issuing the guidance in final form, FDA undertake a much broader review of existing sources of grading scales and a more deliberative consultation process with interested parties. In-depth discussions with vaccine research experts and experts in adverse event analysis, both at NIH and elsewhere, would enhance the clarity, utility, and applicability of the guidance and reduce the chances of unintended negative consequences. In the sections below, we discuss general and specific concerns and comment on a number of elements of the clinical and laboratory parameters outlined in Tables A and B.

General Concerns

Rationale for Separate Toxicity Scale for Healthy Subjects. While we agree that a lower tolerance of risk is necessary in vaccine studies with healthy volunteers, the guidance does not provide sufficient rationale for the need for a separate toxicity scale, as opposed to the use of a more generally applicable scale, combined with specific criteria for inclusion/exclusion and stopping rules that are appropriate to the nature of the study. The guidance should explain in further detail why FDA believes that a separate and specific scale for healthy volunteers in preventive vaccines trials is the preferred approach.

In clarifying the need for a separate scale, there are two issues relating to the scope of the guidance that need to be addressed. First, a rationale is needed for a scale for healthy versus other volunteers, and second, justification is needed for application to vaccine trials and not to other trials with healthy volunteers.

In many cases, volunteers in such trials may be healthy in terms of some of the narrow baseline criteria, but they may not be healthy in terms of all of the parameters. For example, the grade 1 parameters are all set very close to normal levels, which is likely to create confusion when values are slightly elevated for reasons unrelated to vaccine administration. Patients may occasionally have small abnormalities that are clinically non-relevant. Parameters set too tightly could exclude many volunteers due to insignificant abnormalities. The creation of extremely narrow inclusion criteria has significant implications for the ability to study representative population samples and for generalizability of research results. Also, in many cases, populations facing a high risk of the disease under study would effectively be excluded from trials of preventive vaccines, thus making the trials less efficient (larger samples size and/or longer follow-up would be needed to accumulate a sufficient number of positive endpoints in a trial), and trials might potentially be less relevant to the eventual user population.

Uses of the Toxicity Scale and Relationship to Adverse Events. It would be helpful to clarify the range of uses for the proposed scale and to amplify on how the toxicity scales relate to adverse event reporting. For example, it would be helpful to provide further explanation about how the scale is to be applied to adverse event reporting and what impact it will have on reporting. It

appears to us that the number and nature of adverse reports could be dramatically different using this scale, compared to existing scales that set broader ranges for the different levels of deviation from baseline values. Would separate criteria be developed for adverse event reporting with healthy volunteers, and, if so, is there a broad consensus that this would be a desirable approach? It might be advisable to conduct a pilot study of the application of the toxicity scale, using data from completed vaccine trials, in order to compare the use of this draft scale to safety reporting using existing procedures, and determine if there is additional value from the use of a separate scale in specific kinds of research trials. Also, it would be important to consider how the scale relates to existing vaccine safety reporting efforts such as the joint FDA/CDC Vaccine Adverse Event Report System (VAERS)¹ and the related CDC Vaccine Safety Datalink Project.² If there is a need to consider mild toxicities from vaccines at a greater level of sensitivity than that used to detect such abnormalities in other kinds of research, the uses of this information should be made more explicit. If, on the other hand, mild deviations from baseline values are important in all research, then a different set of scales may not be warranted.

Implications for Enrollment Criteria, Recruitment, Stopping Rules, and Adverse Events. We have concerns about the impact of the baseline values outlined in the grading scales on study enrollment criteria, recruitment, stopping rules, and adverse events and urge that further analysis and discussion of this issue. If the enrollment criteria are linked to the specific scales used for grading of adverse events, a separate scale for healthy volunteers in vaccine trials will result in different enrollment criteria in these, compared to other studies. Sponsors and researchers may find that narrow ranges for toxicity reporting, as outlined in the draft guidance, will hinder their ability to conduct research with populations that have preexisting morbidities unrelated to the vaccine in question. Also, the narrowness of the criteria for each grade has implications for stopping rules and for enrollment of patients with mild abnormalities. For example, some clinicians would not consider a 40.1 C fever after a vaccination potentially life-threatening; also, many vaccine study volunteers might wish to enroll in a trial with grade 2 non-fasting hyperglycemia or grade 2 hypotension. It would be unfortunate if well-designed vaccine trials were stopped based on grade 3 stopping criteria that might only reflect pre-existing conditions. Eating sugary foods 30 minutes prior to the blood-draw in a person with reduced glucose tolerance or a measurement of systolic blood pressure of 79 mm Hg in perfect health could result in severe adverse events with the suggested guidelines. While we agree that risk tolerance in trials with healthy volunteers must be very low, the ranges in other guidelines may be more appropriate to actual clinical trial practice.

As mentioned above, this issue has philosophical and scientific implications. How broad a range of subjects should be enrolled in vaccine trials? What level of risk is acceptable? How much should researchers strive to conduct clinical trials that are generalizable to the wide range of eventual users of the vaccine? These issues require further analysis and consultation with scientific experts, both in the public and private sector, engaged in research in different settings and disease areas. A more complete assessment of the impact of these baseline values in different types of vaccine trials is needed.

¹ <http://www.fda.gov/cber/vaers/vaers.htm>

² <http://www.cdc.gov/nip/vacsafe/vsd/default.htm#Data>

Need for Further Discussion and Input. A more comprehensive review and discussion of other grading tables is needed to put the FDA guidance into context and to explain how and why a different approach is being taken in the draft guidance. Other such guidelines include FDA's own *Guideline for Industry Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* as well as guidelines developed by NIH components, e.g., the Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases and the National Cancer Institute (NCI). DAIDS recently issued a new adverse event grading table which is designed for use in many different trial settings, including HIV treatment, prevention, and vaccine trials (Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events). Since many different trials may be conducted at one DAIDS site, it is important in this area of research to use one harmonized set of reporting criteria.

It may be desirable for FDA and NIH to hold a joint workshop to discuss scientific issues raised in the draft guidance, to further explore the implications of the use of different scales in different kinds of research, and in order to exchange information on the diverse portfolio of research studies that might be affected by the FDA guidance.

Specific Comments

Scales and Baseline Values. We have two types of concerns about the scales and the baseline values used to define the four grades. First, the ranges for mild, moderate, severe and life-threatening are too stringent, i.e., deviations from normal laboratory values or other baseline measurements in some cases are rated as more severe in this guidance than they would be by most clinicians. Second, applying the guidance to populations that have wider variations in baseline values will be difficult. These populations are often important to include in preventive vaccine trials due to their high risk of exposure to the disease under study.

The need for a wider range of baseline values in preventive vaccine trials must be balanced with the need to approach risk very conservatively in prevention trials with healthy individuals. Therefore, the construction of the baseline ranges may have implications for inclusion/exclusion criteria which in turn involve a number of scientific judgments about how wide a range of participants should be enrolled in a trial. Selection of baseline values may lead to specific decisions about what medical conditions should be used as exclusion criteria, and in some cases could limit generalizability of study findings to broader population groups.

In relation to the grading of various deviations from baseline, setting the threshold for classification of events as severe or life-threatening too low, may cause important vaccine trials to be terminated due to severe adverse events. Setting the threshold too high may pose unacceptable risks, particularly in healthy populations. Further review of the evidence from specific vaccine trials in different populations would be useful in helping determine whether the values set forth in the guidance provide an appropriate balance between caution and flexibility.

Consistency with Other Scales. Some of the laboratory values and other parameters are defined more conservatively than in existing guidelines used by NIH. For example, the criteria in DAIDS new AE Grading Table are considerably less restrictive than those in the proposed FDA guidance (please see Attachment I which provides a side-by-side comparison of the two guidances and analyzes the specific differences between them). The differences between the

FDA parameters and the existing DAIDS scale, as well as other toxicity scales used in NIH vaccine trials, are significant in terms of the range of values considered to be normal or mild, versus more severe. Also, the DAIDS scale includes a much broader range of clinical parameters, which are relevant to different types of DAIDS trials.

Applicability to Populations with Pre-existing Abnormalities. Some consideration should be given to adding language to the guidance that would allow for an alteration of the grading scale for populations with pre-existing abnormalities, such as diabetes, renal and liver disease. In these situations abnormalities may be present before vaccination, and scales for assessing adverse events should be modified accordingly. Thus, in patients with renal disease who have elevations in serum BUN and creatinine, scales for defining mild, moderate and severe toxicity for these parameters should be specifically modified using changes from baseline which can be expressed as multiples of the upper limit of the normal range. Similarly in patients with liver disease or pre-existing elevations in serum aminotransferase or alkaline phosphatase levels, scales for adverse events should be modified and based upon changes from baseline. The currently recommended grading scales should not be used to exclude populations from study of vaccine effects and safety, particularly since these populations are often at risk for the conditions meant to be prevented by vaccination.

Applicability to International Populations. In international studies, the baseline values are frequently outside the normal reference limits for U.S. populations, particularly in areas such as hematology and blood chemistry. Therefore, it is important to consider what the appropriate reference range should be for a given population. Many international studies of vaccines may be particularly relevant to the risk of disease faced by these populations, yet the narrow ranges of laboratory values might exclude the most relevant population groups. This raises the question of whether a local baseline standard should be used in some cases.

Terminology and Definitions. The guidance should define an age range for “adolescent.” In addition, to provide further uniform criteria, some of the parameters, such as fatigue and myalgia, should be defined.

References. Two of the references are outdated and should be changed. The NCI Common Toxicity Criteria reference is out of date. The criteria were revised in December 2003, and the document is now called the “Common Terminology Criteria for Adverse Events v3.0 (CTCAE).” Please use the reference: National Cancer Institute Common Terminology for Adverse Events Dec 12, 2003 (<http://ctep.cancer.gov/reporting/CTCAEv3.pdf>). The DAIDS AE Grading Table reference is outdated. Please refer to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0 (Publish Date: December, 2004).

Specific Comments on Table A for Clinical Abnormalities

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Interferes with activity or repeated use of non-narcotic pain reliever	Prevents daily activity or repeated use of narcotic pain reliever	Emergency room (ER) visit or hospitalization
Tenderness	Mild pain to touch	Pain with movement	Significant pain at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

- Add a table(s) for “Other Reactions” that can be seen after immunization that would address toxicities such as, but not limited to, urticaria, pruritus, rash, dyspnea, arthralgias / arthritis, induration, bruising.
- An “ER visit” or hospitalization is used to define Grade 4 for several of the clinical categories. Emergency room visit or hospitalization may not accurately reflect truly life-threatening events. In the US, individuals without medical coverage often utilize emergency room visits for routine ambulatory care. In contrast, in resource poor countries, hospitalization for life-threatening events may not be available on account of inability to pay.
- Add guidance for grading allergic reactions.
- For injection site reactions, it is not clear why the local reaction toxicity assessment is broken down into erythema and swelling. How would a site reaction be graded if it became ulcerated, or infected or became a sterile abscess and drained, or developed post injection phlebitis?
- For tenderness, the Definition for Grade 2 would be appropriate for Grade 1; definition for Grade 3 would be appropriate for Grade 2; there is no “life threatening” tenderness, therefore, a “not applicable” should be inserted under Grade 4.
- For erythema/redness, recommend up to 9 cm diameter for Grade 1; greater than 9 cm for Grade 2; ulceration requiring medical treatment for Grade 3; and significant reactions associated with necrosis and requiring medical treatment or hospitalization for Grade 4.
- For pain and headache, how will taking a single dose of a narcotic pain reliever be graded?

Vital Signs *	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F)	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) - mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate - breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

- Fever scales should be 98.8° - 102°F for Grade 1; 102° - 104°F for Grade 2; 104° - 106°F for Grade 3; and 106°F for Grade 4.
- The gradients for hypertension should be: systolic Grade 1 up to 160; Grade 2 up to 180; and Grade 3 >180.
- Regarding respiratory rate, rate alone is not as meaningful an indicator as more specific symptoms such as cough, bronchospasm and dyspnea. If respiratory rate is included, the "potentially life threatening" category for respiratory rate should be ">25 and not responsive to oxygen administration" rather than "intubation." If a patient is wheezing, it is common to try to avoid intubation, but it is still a life threatening condition.
- Recognizing the difficulty that exists in trying to "standardize" vital signs and assign absolute cutoffs, and given the high degree of intrinsic normal variability among different people and their vital signs at their baseline, this scheme will capture many individuals who are not experiencing any "true abnormalities." They will be reported as experiencing toxicity from the vaccine product. This concern applies to most of the vital signs, particularly bradycardia, hypertension, hypotension and respiratory rate. Also, since all of the systolic BP measurements would meet the criteria for intravenous fluid hydration and/or hospitalization for the administration of pressor agents, they could arguably be classified as grade 4 toxicities. One way to circumvent the inter-patient variability is to record changes in parameters from their baseline or initial pre-vaccine visit. Additionally, it might be valuable to determine whether individuals with vital signs recorded here are experiencing any symptoms associated with their "toxicity." For example, respirations of 25 and shortness of breath; bradycardia of 45 and chest pain. Finally, consider modifying the hypotension criteria

to reflect that only symptomatic patients will be included and perhaps also changes from an individual's baseline.

Systemic (General)	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/ 24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Headache	No interference with activity	Some interference with activity or repeated use of non-narcotic pain reliever	Significant, prevents daily activity or repeated use of narcotic pain reliever	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization

Systemic illness	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulation)	No interference with activity	Some interference with activity not requiring medical intervention.	Prevents daily activity and requires medical intervention	ER visit or hospitalization

- Delete “illness” in the statement “Illness or clinical adverse event (as defined according to applicable regulation)” because there are no illnesses whose definitions are regulated.
- There is nothing in the tables relevant to the neurologic exam other than headache. A scale for the neurologic exam should be included, at least for level of consciousness and deep tendon reflexes.
- Aseptic meningitis and encephalitis are described as complications of vaccines, but the symptoms are not described in any of the tables.
- For vomiting and diarrhea, the grading should refer to symptomatic effects rather than measurements that might be impossible to perform or would vary from person to person based on size, weight, co-morbidities at baseline, etc. For diarrhea, weights of output are not relevant for healthy volunteers. On a practical level, it is doubtful that weights for 24-hour stool losses will be available in non-hospitalized subjects.

- Consider adding other systemic reactions, such as anorexia, dizziness, rash, allergic reaction, and systemic immunologic reactions not listed (rash/urticaria/anaphylaxis). Swelling is mentioned but only in relation to local injection site.
- Nausea/vomiting should be divided into two categories since they are two distinct symptomologies, and the latter can be quantified with measurable production of vomitus whereas nausea is subjective. Also, two episodes of vomiting in 24 hours should be considered more than mild.
- With regard to the scale for headache, it is not clear how a one-time use of non-narcotic pain reliever would be scored? (Grade 2 is repeated use; Grade 1 does not refer to use.)
- For other clinical abnormalities not included in the grading table, the guidance should clarify that the definitions used for “systemic illness” could be used to define the severity of those abnormalities. In other words, grade 1 abnormalities would be defined as “no interference with activity;” grade 2 abnormalities would be those with “some interference with activity not requiring medical intervention;” grade 3 abnormalities would be those that “prevent daily activity and require medical intervention.” The definition for grade 4 abnormalities should be reconsidered, given the difficulty in using “ER visit” as a criterion, as we have described above. Rather than using “ER visit” as part of the definition of a grade 4 abnormality, a preferable alternative is “Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death” (see DAIDS scale under “Clinical adverse event NOT identified elsewhere in the table”).

Specific Comments on Table B

The second sentence in the prefatory statement should be revised as follows: “Institutional normal reference ranges should be provided *in the protocol or other suitable document* to demonstrate that they are appropriate.”

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125 or abnormal sodium with clinical signs #
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia				Insulin requirements or hyperosmolar coma
Fasting – mg/dL	100 – 110	111 – 125	>125	
Random – mg/dL	110 – 125	126 – 200	>200	
Blood Urea Nitrogen	23 – 26	27 – 31	> 31	Requires dialysis
BUN mg/dL				
Creatinine - mg/dL	1.1 – 1.5	1.6 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein –Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.0 – 10 x ULN	> 10 x ULN
Liver Function Tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

The clinical signs of an abnormal elevation or decline should be described for each laboratory parameter to be monitored in the study.

** “ULN” is the upper limit of the normal range.

- Many of the Grade 4 parameters are not truly life-threatening. This seems to change the meaning of the term “Grade 4,” particularly for some lab tests (e.g., a Grade 4 potassium is

this table could be a Grade 1 in the DAIDS AE Grading Table). For hyperkalemia, the Grade 4 category should be “>5.6 with arrhythmia.”

- In many case, a number of laboratory values have to be based on local norms. Several of these criteria (e.g. hemoglobin and ANC) are too strict for some ethnic minorities, and will make international trials much more difficult.
- For laboratory parameters that have tendency to fluctuate in the absence of clinical abnormalities, Grade 1 should not start at 1.1 x ULN. For example, bilirubin, amylase, ALT / AST.
- For laboratory parameters assessed as multiples of ULN, the lower limits of each grade should be adjusted so as to prevent values that fall between two grades. For example: Grade 1 = 1.1 – 2.0 x ULN; Grade 2 = >2.0 – 3.0 x ULN. (Definitions using multiplier functions are mathematically incorrect as written, leaving a gap with some numbers falling between grades.)
- The following parameters are considered to be graded too strictly (see DAIDS AE Grading Table in comparison): Hyponatremia, hyperkalemia, BUN, CPK, albumin, total protein, cholesterol, hemoglobin (and Grade 1 is normal in many labs), Grade 1 and 2 WBC decrease, Grade 1 and 2 platelet decrease, PT, PTT, fibrinogen both increase and decrease, and urinary protein.
- Hyperglycemia is not relevant without symptoms. For hyperglycemia, the definitions are set too low. See DAIDS AE Grading Table for comparison.
- Creatinine scale should be based on site’s ULN, as measurement is variable according to laboratory. Suggest Grade 1 = >ULN-2; Grade 2 = >2-2.5; Grade 3 = >2.5; Grade 4 = requiring dialysis.
- Alkaline phosphatase (if needed) should be graded in the same way as ALT and AST.
- About 8 to 9 percent of individuals have asymptomatic Gilbert’s syndrome. For bilirubin when LFTs are normal, it seems unreasonable to exclude those individuals based on a bilirubin measurement alone.

Hematology *	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	12.0 – 13.0	10.0 – 11.9	8.0 – 9.9	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dl	12.5 – 14.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm ³	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm ³	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm ³	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm ³	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm ³	650 – 1500	1501 – 5000	> 5000	Hypereosinophilic syndrome
Platelets Decreased - cell/mm ³	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** “ULN” is the upper limit of the normal range.

Urine *	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	>2+
Glucose	Trace	1+	2+	>2+
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 – 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

- Hypereosinophilic syndrome is a disease based on multiple criteria. This should not be listed when the rest of parameter is based on eosinophil count alone. Eosinophil count will be another factor that is highly based on locale, and the current criteria will create undue problems for international sites. The norms should be dictated by the testing site and be relevant to healthy adults in that region.
- For urine blood, 1-5 RBC/hpf is normal and should not be considered Grade 1. Start Grade 1 at 6-10 RBS/hpf; and Grade 2 >10 RBS/hpf. For vaccine evaluation in healthy adults, the only measurement of relevance in the UA is the presence or absence of granular casts and

possibly glucose. Those should be assessed and creatinine as the measure of renal inflammation and function.

- Consider the possible addition of prothrombin time/international normalized ratio (INR).
- It would be important to take into consideration the technical and quality control factors that affect diagnostic test accuracy and that, with appropriate consultation, this is reflected in many of the Grade 1 guidelines. Reconsider the grading scale for protein in the urine. Dipstick urinalysis is convenient, but false-positive and false-negative results can occur. Trace protein is quite common; more so, most clinicians would not consider >+2 protein as life-threatening.

**Comparison of DAIDS AE Grading Table and
FDA Draft Guidance on Toxicity Grading Scale for Healthy Adult and Adolescent
Volunteers Enrolled in Preventive Vaccine Clinical Trials**

Clinical Abnormalities

PARAMETER Injection site pain	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 4				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
FDA Draft Guidance – Page 3				
Pain	Does not interfere with activity	Interferes with activity or repeated use of non-narcotic pain reliever	Prevents daily activity or repeated use of narcotic pain reliever	Emergency room (ER) visit or hospitalization
Tenderness	Mild pain to touch	Pain with movement	Significant pain at rest	ER visit or hospitalization

Comments:

- The draft guidance refers to the use of narcotics, and the DAIDS AE grading table does not.

PARAMETER Injection site reaction (localized)	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 4				
Injection site reaction (localized) Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm ² – 81cm ²)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm ²)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
FDA Draft Guidance – Page 3				
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative Dermatitis
Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

Comments:

- The draft guidance values for Grade 1 are smaller than the DAIDS AE grading table.
- The values for Grade 2 and Grade 4 are similar in both documents.
- For Grade 3, the DAIDS AE grading table lists specific conditions, whereas the draft guidance uses size values.
- For swelling, the draft guidance references to daily activities, and the DAIDS AE grading table does not.

PARAMETER Fever (nonaxillary)	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 3				
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
FDA Draft Guidance – Page 4				
Fever (°C) **	38.0 – 38.4	38.5 – 38.9	39.0 – 40	> 40
(°F)	100.4 – 101.1	101.2 – 102.0	102.1 – 104	> 104

Comments:

- No significant difference between the two documents.

PARAMETER Hypertension	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 6				
Hypertension Adult > 17 years (with repeat testing at same visit)	> 140 – 159 mmHg systolic OR > 90 – 99 mmHg diastolic	> 160 – 179 mmHg systolic OR > 100 – 109 mmHg diastolic	> 180 mmHg systolic OR > 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
FDA Draft Guidance – Page 4				
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension

Comments:

- The value ranges for Grade 1 are similar in both documents.
- The value ranges for Grades 2 and 3 in the draft guidance are lower than the DAIDS AE grading table.
- The value for Grade 4 is similar in both documents.

PARAMETER Hypotension	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 6				
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
FDA Draft Guidance – Page 4				
Hypotension (systolic) - mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock

Comments:

- For Grades 1 – 3 in the draft guidance, actual values are listed; values are not listed in the DAIDS AE grading table.
- The value Grade 4 is similar in both documents, however, the draft guidance refers to ER visit or hospitalization, and the DAIDS AE grading table does not.

PARAMETER Nausea/vomiting	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 9				
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
FDA Draft Guidance – Page 4				
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock

Comments:

- No significant difference between the two documents, however, the draft guidance refers to ER visit or hospitalization, and the DAIDS AE grading table does not.

PARAMETER Diarrhea	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 8				
Diarrhea Adult and Pediatric ≥ 1 year	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
FDA Draft Guidance – Page 4				
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration hypotensive shock	ER visit or hospitalization for hypotensive shock

Comments:

- The value ranges for Grades 1 - 3 are similar, however, the draft guidance includes weight of stools, and the DAIDS AE grading table does not.
- The value for Grade 4 is similar in both documents, however, the draft guidance refers to ER visit or hospitalization, and the DAIDS AE grading table does not.

PARAMETER Headache	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 10				
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
FDA Draft Guidance – Page 4				
Headache	No interference with activity	Some interference with activity or repeated use of nonnarcotic pain reliever	Significant, prevents daily activity or repeated use of narcotic pain reliever	ER visit or hospitalization

Comments:

- The values for Grade 1 and Grade 3 are similar in both documents.
- For Grade 2, the draft guidance refers to the use of narcotics, and the DAIDS AE grading table does not.
- The value for Grade 4 is similar in both documents, however, the draft guidance refers to ER visit, and the DAIDS AE grading table does not.

PARAMETER Fatigue	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 3				
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
FDA Draft Guidance – Page 4				
Fatigue	No interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization

Comments:

- No significant difference between the two documents, however, the draft guidance refers to ER visit or hospitalization, and the DAIDS AE grading table does not.

PARAMETER Myalgia	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 13				
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
FDA Draft Guidance – Page 4				
Myalgia	No interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization

Comments:

- No significant difference between the two documents, however, the draft guidance refers to ER visit or hospitalization, and the DAIDS AE grading table does not.

PARAMETER General	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 3				
Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
FDA Draft Guidance – Page 5				
Illness or clinical adverse event (as defined according to applicable regulation)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Comments:

- The value for Grade 1 is similar in both documents.
- For Grades 2 and 3, the draft guidance refers to medical intervention, and the DAIDS AE grading table does not.
- For Grade 4, the draft guidance refers to ER visit or hospitalization, and the DAIDS AE grading table does not

Laboratory Parameters

PARAMETER Sodium, serum, low	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 19				
Sodium, serum, low	130 – 135 mEq/L 130 – 135 mmol/L	125 – 129 mEq/L 125 – 129 mmol/L	121 – 124 mEq/L 121 – 124 mmol/L	≤ 120 mEq/L ≤ 120 mmol/L
FDA Draft Guidance – Page 6				
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125 or abnormal sodium with clinical signs

Comments:

- No significant difference between the two documents.

PARAMETER Sodium, serum, high	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 19				
Sodium, serum, high	146 – 150 mEq/L 146 – 150 mmol/L	151 – 154 mEq/L 151 – 154 mmol/L	155 – 159 mEq/L 155 – 159 mmol/L	≥ 160 mEq/L ≥ 160 mmol/L
FDA Draft Guidance – Page 6				
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150

Comments:

- The draft guidance values start in Grade 1 as comparable to the DAIDS AE grading table, but with each successive Grade, it becomes more noticeable that the draft guidance values are lower than the DAIDS AE grading table values.

PARAMETER Potassium, serum, high	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 19				
Potassium, serum, high	5.6 – 6.0 mEq/L 5.6 – 6.0 mmol/L	6.1 – 6.5 mEq/L 6.1 – 6.5 mmol/L	6.6 – 7.0 mEq/L 6.6 – 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
FDA Draft Guidance – Page 6				
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6

Comments:

- The draft guidance values are lower than the DAIDS AE grading table values.

PARAMETER Potassium, serum, low	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 19				
Potassium, serum, low	3.0 – 3.4 mEq/L 3.0 – 3.4 mmol/L	2.5 – 2.9 mEq/L 2.5 – 2.9 mmol/L	2.0 – 2.4 mEq/L 2.0 – 2.4 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
FDA Draft Guidance – Page 6				
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1

Comments:

- The draft guidance values are higher than the DAIDS AE grading table values.

PARAMETER Glucose, serum, low	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 19				
Glucose, serum, low Adult and Pediatric ≥ 1 month	55 – 64 mg/dL 3.05 – 3.55 mmol/L	40 – 54 mg/dL 2.22 – 3.00 mmol/L	30 – 39 mg/dL 1.67 – 2.16 mmol/L	< 30 mg/dL < 1.67 mmol/L
FDA Draft Guidance – Page 6				
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45

Comments:

- The draft guidance values are higher than the DAIDS AE grading table values.

PARAMETER Glucose, serum, high	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 18				
Glucose, serum, high Nonfasting	116 – 160 mg/dL 6.44 – 8.88 mmol/L	161 – 250 mg/dL 8.94 – 13.88 mmol/L	251 – 500 mg/dL 13.93 – 27.75 mmol/L	> 500 mg/dL > 27.75 mmol/L
Fasting	110 – 125 mg/dL 6.11 – 6.94 mmol/L	126 – 250 mg/dL 6.99 – 13.88 mmol/L	251 – 500 mg/dL 13.93 – 27.75 mmol/L	> 500 mg/dL > 27.75 mmol/L
FDA Draft Guidance – Page 6				
Glucose – Hyperglycemia				
Fasting – mg/dL	100 – 110	111 – 125	> 125	Insulin requirements or hyperosmolar coma
Random – mg/dL	110 – 125	126 – 200	> 200	

Comments:

- The draft guidance values for “Fasting” are much lower than the DAIDS AE grading table values.
- It appears the “Random” values in the draft guidance would compare with “Nonfasting” in the DAIDS AE grading table. The “Random” values are much lower than the DAIDS AE grading table values.
- For Grade 4, the draft guidance refers to medical intervention or a clinical sign, which the DAIDS AE grading table does not use in the laboratory section.

PARAMETER Creatinine	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 18				
Creatinine	1.1 – 1.3 x ULN [†]	1.4 – 1.8 x ULN [†]	1.9 – 3.4 x ULN [†]	≥ 3.5 x ULN [†]
FDA Draft Guidance – Page 6				
Creatinine – mg/dL	1.1 – 1.5	1.6 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis

Comments:

- The draft guidance values start in Grade 1 as comparable to the DAIDS AE grading table, but with each successive Grade, it becomes more noticeable that the draft guidance values are lower than the DAIDS AE grading table values.
- Grade 4 in the draft guidance refers to dialysis, and the DAIDS AE grading table does not.

PARAMETER Calcium, serum, low	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 18				
Calcium, serum, low (corrected for albumin) Adult and Pediatric ≥ 7 days	7.80 – 8.40 mg/dL 1.95 – 2.10 mmol/L	7.00 – 7.70 mg/dL 1.75 – 1.93 mmol/L	6.10 – 6.90 mg/dL 1.53 – 1.73 mmol/L	< 6.10 mg/dL < 1.53 mmol/L
FDA Draft Guidance – Page 6				
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0

Comments:

- The draft guidance values start in Grade 1 as comparable to the DAIDS AE grading table, but with each successive Grade, it becomes more noticeable that the draft guidance values are higher than the DAIDS AE grading table values.

PARAMETER Calcium, serum, high	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 18				
Calcium, serum, high (corrected for albumin) Adult and Pediatric ≥ 7 days	10.60 – 11.50 mg/dL 2.65 – 2.88 mmol/L	11.60 – 12.50 mg/dL 2.90 – 3.13 mmol/L	12.60 – 13.50 mg/dL 3.15 – 3.38 mmol/L	> 13.50 mg/dL > 3.38 mmol/L
FDA Draft Guidance – Page 6				
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0

Comments:

- The draft guidance values start in Grade 1 as comparable to the DAIDS AE grading table, but with each successive Grade, it becomes more noticeable that the draft guidance values are lower than the DAIDS AE grading table values.

PARAMETER Magnesium, serum, low	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 19				
Magnesium, serum, low	1.20 – 1.40 mEq/L <i>0.60 – 0.70 mmol/L</i>	0.90 – 1.10 mEq/L <i>0.45 – 0.55 mmol/L</i>	0.60 – 0.80 mEq/L <i>0.30 – 0.40 mmol/L</i>	< 0.60 mEq/L < 0.30 mmol/L
FDA Draft Guidance – Page 6				
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9

Comments:

- The draft guidance values are higher than the DAIDS AE grading table values.

PARAMETER Phosphate, serum, low	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 19				
Phosphate, serum, low Adult and Pediatric > 14 years	2.50 mg/dL – < LLN <i>0.81 mmol/L – < LLN</i>	2.00 – 2.40 mg/dL <i>0.65 – 0.78 mmol/L</i>	1.00 – 1.90 mg/dL <i>0.32 – 0.61 mmol/L</i>	< 1.00 mg/dL < 0.32 mmol/L
FDA Draft Guidance – Page 6				
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6

Comments:

- The draft guidance values start in Grade 1 as comparable to the DAIDS AE grading table, but with each successive Grade, it becomes more noticeable that the draft guidance values are higher than the DAIDS AE grading table values.

PARAMETER Creatine Kinase	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 18				
Creatine Kinase	3.0 – 5.9 x ULN	6.0 – 9.9 x ULN	10.0 – 19.9 x ULN	≥ 20.0 x ULN
FDA Draft Guidance – Page 6				
CPK – mg/dL	1.25 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN

Comments:

- The draft guidance values are lower than the DAIDS AE grading table values.

PARAMETER Albumin, serum, low	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 17				
Albumin, serum, low	3.0 g/dL – < LLN 30 g/L – < LLN	2.0 – 2.9 g/dL 20 – 29 g/L	< 2.0 g/dL < 20 g/L	NA
FDA Draft Guidance – Page 6				
Albumin – hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--

Comments:

- No significant difference between the two documents.

PARAMETER Alkaline Phosphatase	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 17				
Alkaline Phosphatase	1.25 – 2.50 x ULN	2.60 – 5.00 x ULN	5.10 – 10.00 x ULN	> 10.00 x ULN
FDA Draft Guidance – Page 6				
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.0 – 10 x ULN	> 10 x ULN

Comments:

- The value range for Grade 1 is similar in both documents.
- The value range for Grade 2 is much narrower in the draft guidance than the DAIDS AE grading table.
- The value range for Grade 3 is much broader in the draft guidance than the DAIDS AE grading table.
- The value range for Grade 4 is the same in both documents.

PARAMETER LFTs – ALT/AST	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 17				
ALT (SGPT)	1.25 – 2.50 x ULN	2.60 – 5.00 x ULN	5.10 – 10.00 x ULN	> 10.00 x ULN
AST (SGOT)	1.25 – 2.50 x ULN	2.60 – 5.00 x ULN	5.10 – 10.00 x ULN	> 10.00 x ULN
FDA Draft Guidance – Page 6				
Liver Function Tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

Comments:

- No significant difference between the two documents.

PARAMETER Bilirubin (Total)	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 17				
Bilirubin (Total) Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
FDA Draft Guidance – Page 6				
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN

Comments:

- The draft guidance values for bilirubin accompanied by increase in LFTs are lower than the DAIDS AE grading table values.
- The draft guidance values for bilirubin when LFT is normal start in Grade 1 as comparable to the DAIDS AE grading table, but with each successive Grade, it becomes more noticeable that the draft guidance values are higher than the DAIDS AE grading table values.

PARAMETER Cholesterol (fasting)	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 18				
Cholesterol (fasting) Adult ≥ 18 years	200 – 239 mg/dL 5.18 – 6.19 mmol/L	240 – 300 mg/dL 6.22 – 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
FDA Draft Guidance – Page 6				
Cholesterol	201 – 210	211 – 225	> 226	--

Comments:

- The draft guidance values are lower than the DAIDS AE grading table values.

PARAMETER Lipase	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 19				
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
FDA Draft Guidance – Page 6				
Pancreatic enzymes – lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

Comments:

- No significant difference between the two documents.

PARAMETER Hemoglobin (Hgb)	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 16				
Hemoglobin (Hgb) Adult and Pediatric ≥ 57 days (HIV <u>POSITIVE</u> ONLY)	8.50 – 10.00 g/dL 1.32 – 1.55 mmol/L	7.50 – 8.40 g/dL 1.16 – 1.30 mmol/L	6.50 – 7.40 g/dL 1.01 – 1.15 mmol/L	< 6.50 g/dL < 1.01 mmol/L
Adult and Pediatric ≥ 57 days (HIV <u>NEGATIVE</u> ONLY)	10.00 – 10.90 g/dL 1.55 – 1.69 mmol/L OR Any decrease 2.50 – 3.40 g/dL 0.39 – 0.53 mmol/L	9.00 – 9.90 g/dL 1.40 – 1.53 mmol/L OR Any decrease 3.50 – 4.40 g/dL 0.54 – 0.68 mmol/L	7.0 – 8.90 g/dL 1.09 – 1.38 mmol/L OR Any decrease ≥ 4.50 g/dL ≥ 0.70 mmol/L	< 7.00 g/dL < 1.09 mmol/L
FDA Draft Guidance – Page 7				
Hemoglobin (Female) - gm/dL	12.0 – 13.0	10.0 – 11.9	8.0 – 9.9	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dl	12.5 – 14.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0

Comments:

- The draft guidance breaks the values out into male and female; the DAIDS AE grading table does not.
- The draft guidance values are higher than the DAIDS AE grading table values for both HIV + and HIV -, including the “decrease” values.

PARAMETER WBC, decreased	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 17				
WBC, decreased	2,000 – 2,500/mm ³ 2.000×10^9 – 2.500×10^9 /L	1,500 – 1,999/mm ³ 1.500×10^9 – 1.999×10^9 /L	1,000 – 1,499/mm ³ 1.000×10^9 – 1.499×10^9 /L	< 1,000/mm ³ < 1.000×10^9 /L
FDA Draft Guidance – Page 7				
WBC Decrease – cell/mm ³	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000

Comments:

- The value ranges for Grades 1 and 2 in the draft guidance are higher than the DAIDS AE grading table value ranges.
- The value ranges for Grades 3 and 4 are the same in the two documents.

PARAMETER Absolute lymphocyte count	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 16				
Absolute lymphocyte count – Adult and Pediatric > 13 years (HIV <u>NEGATIVE</u> ONLY)	600 – 650/mm ³ 0.600×10^9 – 0.650×10^9 /L	500 – 599/mm ³ 0.500×10^9 – 0.599×10^9 /L	350 – 499/mm ³ 0.350×10^9 – 0.499×10^9 /L	< 350/mm ³ < 0.350×10^9 /L
FDA Draft Guidance – Page 7				
Lymphocytes Decrease – cell/mm ³	750 – 1,000	500 – 749	250 – 499	< 250

Comments:

- The value ranges for Grade 1 in the draft guidance are higher than the DAIDS AE grading table value ranges.
- The value ranges for Grade 2 are similar in both documents.
- The value ranges for Grades 3 and 4 in the draft guidance are lower than the DAIDS AE grading table value ranges.

PARAMETER Absolute neutrophil count (ANC)	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 16				
Absolute neutrophil count (ANC) Adult and Pediatric, > 7 days	1,000 – 1,300/mm ³ $1.000 \times 10^9 -$ $1.300 \times 10^9/L$	750 – 999/mm ³ $0.750 \times 10^9 -$ $0.999 \times 10^9/L$	500 – 749/mm ³ $0.500 \times 10^9 -$ $0.749 \times 10^9/L$	< 500/mm ³ < $0.500 \times 10^9/L$
FDA Draft Guidance – Page 7				
Neutrophils Decrease – cell/mm ³	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500

Comments:

- The value ranges for Grades 1 and 2 in the draft guidance are higher than the DAIDS AE grading table value ranges.
- The value range for Grades 3 is similar in both documents.
- The value range for Grade 4 is the same in both documents.

PARAMETER Platelets, decreased	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 17				
Platelets, decreased	100,000 – 124,999/mm ³ $100.000 \times 10^9 -$ $124.999 \times 10^9/L$	50,000 – 99,999/mm ³ $50.000 \times 10^9 -$ $99.999 \times 10^9/L$	25,000 – 49,999/mm ³ $25.000 \times 10^9 -$ $49.999 \times 10^9/L$	< 25,000/mm ³ < $25.000 \times 10^9/L$
FDA Draft Guidance – Page 7				
Platelets Decrease – cell/mm ³	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000

Comments:

- The value ranges for Grades 1, 2, and 3 in the draft guidance are higher than the DAIDS AE grading table value ranges.
- The value range for Grade 4 is the same in both documents.

PARAMETER Prothrombin Time (PT)	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 17				
Prothrombin Time (PT)	1.10 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
FDA Draft Guidance – Page 7				
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN

Comments:

- The draft guidance values are lower than the DAIDS AE grading table values.

PARAMETER Partial Thromboplastin Time (PTT)	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 17				
Partial Thromboplastin Time (PTT)	1.10 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
FDA Draft Guidance – Page 7				
PTT – increase by factor (partial Thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 ULN

Comments:

- The draft guidance values are lower than the DAIDS AE grading table values.

PARAMETER Fibrinogen, decreased	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 16				
Fibrinogen, decreased	100 – 200 mg/dL <i>1.00 – 2.00 g/L</i> OR 0.75 – 0.99 x LLN	75 – 99 mg/dL <i>0.75 – 0.99 g/L</i> OR 0.50 – 0.74 x LLN	50 – 74 mg/dL <i>0.50 – 0.74 g/L</i> OR 0.25 – 0.49 x LLN	< 50 mg/dL < <i>0.50 g/L</i> OR < 0.25 x LLN OR Associated with gross bleeding
FDA Draft Guidance – Page 7				
Fibrinogen decrease – mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

Comments:

- The draft guidance values are higher than the DAIDS AE grading table values.

PARAMETER Proteinuria, random collection	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 20				
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
FDA Draft Guidance – Page 7				
Protein	Trace	1+	2+	> 2+

Comments:

- The draft guidance values are lower than the DAIDS AE grading table values.
- The draft guidance provides a value for Grade 4, and the DAIDS AE grading table does not.

PARAMETER Hematuria (microscopic)	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
DAIDS AE Grading Table – Page 20				
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR RBC casts	Transfusion indicated
FDA Draft Guidance – Page 7				
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 – 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

Comments:

- The value ranges for Grades 1, 2, and 3 in the draft guidance are broader than the DAIDS AE grading table value ranges.
- The value Grade 4 is similar in both documents, however, the draft guidance refers to hospitalization, and the DAIDS AE grading table does not.

Parameters in the FDA Guidance and Not in the DAIDS AE Grading Table

- Tachycardia - beats per minute – Page 4
- Bradycardia - beats per minute – Page 4
- Respiratory Rate – breaths per minute – Page 4
- Blood Urea Nitrogen – BUN mg/dL – Page 6
- Total Protein – Hypoproteinemia g/dL – Page 6
- Pancreatic enzymes – amylase – Page 6
- WBC Increase – cell/mm³ – Page 7
- Eosinophils – cell/mm³ – Page 7
- Fibrinogen increase – mg/dL – Page 7
- Urine – Glucose – Page 7